

10/513699

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<12/04/2007>

Erich Leese

10/513699

***** STN Columbus *****

FILE 'HOME' ENTERED AT 14:52:33 ON 19 DEC 2008

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COST IN U.S. DOLLARS

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ENTRY

SESSION

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0.21

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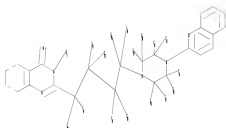
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=>

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chain nodes :
18 22 23 24 25 26 27 28 29 30 31 32 33 34 37 38 39 40 42 43 44
45
ring nodes :
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 46 47 49 50 51 52 53
54 55 56
chain bonds :
7-22 8-18 9-31 11-23 11-24 12-34 13-29 13-30 14-27 14-28 15-47 16-25
16-26 31-32 31-44 31-45 32-33 32-42 32-43 33-34 33-37 33-38 34-39 34-40
ring bonds :
1-2 1-6 2-3 3-4 4-5 5-6 5-7 6-10 7-8 8-9 9-10 11-12 11-16 12-13 13-14
14-15 15-16 46-47 46-52 47-49 49-50 50-51 50-53 51-52 51-56 53-54 54-55
55-56
exact/norm bonds :
1-2 1-6 2-3 3-4 4-5 5-6 5-7 6-10 7-8 7-22 8-9 8-18 9-10 11-12 11-16
11-23 11-24 12-13 12-34 13-14 13-29 13-30 14-15 14-27 14-28 15-16 15-47
16-25 16-26 31-44 31-45 32-42 32-43 33-37 33-38 34-39 34-40
exact bonds :
9-31 31-32 32-33 33-34
normalized bonds :
46-47 46-52 47-49 49-50 50-51 50-53 51-52 51-56 53-54 54-55 55-56
isolated ring systems :
containing 1 : 11 : 46 :

```

G1:H,NH2,Cb,Ak

G2:C,H,Ak

G3:C,N

10/513699

G4:C,H

G5:CH3,NH2

Match level :

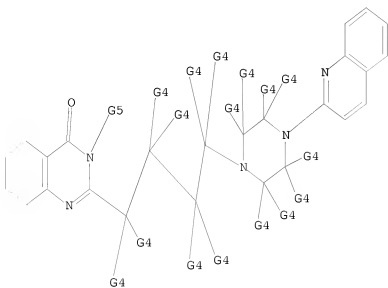
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24:CLASS 25:CLASS 26:CLASS 27:CLASS 28:CLASS 29:CLASS 30:CLASS 31:CLASS
32:CLASS 33:CLASS 34:CLASS 37:CLASS 38:CLASS 39:CLASS 40:CLASS 42:CLASS
43:CLASS 44:CLASS 45:CLASS 46:CLASS 47:CLASS 49:CLASS 50:CLASS 51:CLASS
52:CLASS 53:Atom 54:Atom 55:Atom 56:Atom

L1 STRUCTURE UPLOADED

=> d l1

L1 HAS NO ANSWERS

L1 STR



G1 H, NH2, Cb, Ak

G2 C, H, Ak

G3 C, N

G4 C, H

G5 Me, NH2

Structure attributes must be viewed using STN Express query preparation.

=> s l1 full

FULL SEARCH INITIATED 14:53:22 FILE 'REGISTRY'

FULL SCREEN SEARCH COMPLETED - 74 TO ITERATE

<12/04/2007>

Erich Leese

10/513699

100.0% PROCESSED 74 ITERATIONS 51 ANSWERS
SEARCH TIME: 00.00.01

L2 51 SEA SSS FUL L1

=> file caplus		
COST IN U.S. DOLLARS	SINCE FILE	TOTAL
	ENTRY	SESSION
FULL ESTIMATED COST	178.36	178.57

FILE 'CAPLUS' ENTERED AT 14:53:25 ON 19 DEC 2008
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FILE COVERS 1907 - 19 Dec 2008 VOL 149 ISS 26
FILE LAST UPDATED: 18 Dec 2008 (20081218/ED)

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=> s 12 full
L3 3 L2

=> d ibib abs hitstr tot

L3 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2008:531773 CAPLUS

DOCUMENT NUMBER: 149:118596

TITLE: Biotransformation of
3-amino-5,6,7,8-tetrahydro-2-[4-[4-(quinolin-2-yl)piperazin-1-yl]butyl]quinazolin-4(3H)-one
(TZB-30878), a novel 5-hydroxytryptamine (5-HT)1A
agonist/5-HT3 antagonist, in human hepatic cytochrome
P450 enzymes

AUTHOR(S): Minato, Kouichi; Suzuki, Ryota; Asagarasu, Akira;
Matsui, Teruaki; Sato, Michitaka

CORPORATE SOURCE: Pharmacokinetics Research Department, ASKA
Pharmaceutical Co., Ltd., Kawasaki, Japan

SOURCE: Drug Metabolism and Disposition (2008), 36(5), 831-840
CODEN: DMSDAI; ISSN: 0090-9556

PUBLISHER: American Society for Pharmacology and Experimental
Therapeutics

DOCUMENT TYPE: Journal

LANGUAGE: English

AB 3-Amino-5,6,7,8-tetrahydro-2-[4-[4-(quinolin-2-yl)piperazin-1-yl]butyl]quinazolin-4(3H)-one (TZB-30878), a novel 5-hydroxytryptamine (5-HT)1A agonist/5-HT3 antagonist, is currently under development for the treatment of irritable bowel syndrome. The objective of this investigation was to obtain information on the biotransformation of TZB-30878. This compound has quinazoline, piperazine, and quinoline rings. Metabolites of [quinazoline-2-14C]TZB-30878 were determined using radio high-performance liquid chromatog. on samples obtained after incubation with human hepatic microsomes. Eight metabolites were detected in the microsomal incubation mixture, and their structures were proposed by mass spectrometry techniques using TZB-30878 and two stable labeled TZB-30878 analogs, [quinoline-deuterium (D)6]TZB-30878 and [piperazin-D8]TZB-30878. Liquid chromatog./tandem mass spectrometry analyses suggested that the eight metabolites consisted of a cyclic metabolite (M6), four hydroxylated metabolites (M1, M2, M3, and M4) (three on quinoline ring and one on quinazoline ring), a deaminated metabolite (M5), and two metabolites (M7 and M8) that were presumably intermediates leading to the formation of the cyclic metabolite M6. Hydroxylation sites in the quinoline and quinazoline rings were predicted by electron d. calcns. and confirmed by comparison with authentic stds. To the best of our knowledge, N-deamination by microsomes leading to the formation of M5 appears to be novel. In addition, in vitro expts. in human liver microsomes with cytochrome P 450 (P 450)-specific inhibitors revealed that CYP3A4 was the major enzyme responsible for the metabolism of TZB-30878. Other P 450 enzymes, such as a CYP2D6, played a minor role in its metabolism

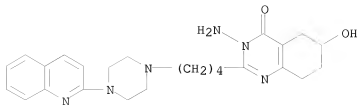
IT 864386-63-0

RL: ANT (Analyte); BSU (Biological study, unclassified); PRP (Properties);
ANST (Analytical study); BIOL (Biological study)

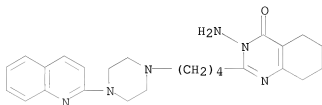
(biotransformation of TZB-30878, novel 5-HT1A agonist/5-HT3 antagonist,
in human hepatic cytochrome P 450 enzymes)

RN 864386-63-0 CAPLUS

CN 4(3H)-Quinazolinone, 3-amino-5,6,7,8-tetrahydro-6-hydroxy-2-[4-[4-(2-quinolinyl)-1-piperazinyl]butyl]- (CA INDEX NAME)



IT 864385-95-5, TZB-30878
 RL: PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (biotransformation of TZB-30878, novel 5-HT1A agonist/5-HT3 antagonist, in human hepatic cytochrome P 450 enzymes)
 RN 864385-95-5 CAPLUS
 CN 4(3H)-Quinazolinone, 3-amino-5,6,7,8-tetrahydro-2-[4-[4-(2-quinolinyl)-1-piperazinyl]butyl]- (CA INDEX NAME)



REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2007:976866 CAPLUS

DOCUMENT NUMBER: 147:461966

TITLE: Pharmacological properties of 3-amino-5,6,7,8-tetrahydro-2-[4-[4-(quinolin-2-yl)piperazin-1-yl]butyl]quinazolin-4(3H)-one (TZB-30878), a novel therapeutic agent for diarrhea-predominant irritable bowel syndrome (IBS) and its effects on an experimental IBS model

AUTHOR(S): Tamaoki, Satoru; Yamauchi, Yukinao; Nakano, Youichi; Sakano, Sayuri; Asagarasu, Akira; Sato, Michitaka

CORPORATE SOURCE: Pharmacological Research Department, ASKA Pharmaceutical Co., Ltd., Shimosakunobe, Takatsu-ku, Kawasaki, Japan

SOURCE: Journal of Pharmacology and Experimental Therapeutics (2007), 322(3), 1315-1323
CODEN: JPETAB; ISSN: 0022-3565

PUBLISHER: American Society for Pharmacology and Experimental Therapeutics

DOCUMENT TYPE: Journal

LANGUAGE: English

AB 3-Amino-5,6,7,8-tetrahydro-2-[4-[4-(quinolin-2-yl)piperazin-1-yl]butyl]quinazolin-4(3H)-one (TZB-30878) is a novel compound with both 5-hydroxytryptamine (5-HT)_{1A} agonism and 5-HT₃ antagonism effects. We hypothesized that TZB-30878 might have benefits from these dual effects as a medication for diarrhea-predominant irritable bowel syndrome (d-IBS), and these studies were designed to confirm the pharmacol. properties of TZB-30878 and its efficacy in an IBS-like animal model. The binding assays demonstrated that [3H]TZB-30878 selectively binds to human 5-HT_{1A} and 5-HT₃ receptors, with K_d values of 0.68±0.03 and 8.90±1.73 nM, resp. Systemic administration of TZB-30878 inhibited 5-HT-induced bradycardia in a dose-dependent manner in rats. In behavioral assays TZB-30878 produced signs of 5-HT syndrome in rats. These results suggest that TZB-30878 has dual effects as a 5-HT_{1A} receptor agonist and a 5-HT₃ receptor antagonist. Finally, we evaluated the effects of TZB-30878 on wrap restraint stress-induced defecation in an IBS-like model in rats. TZB-30878 (1-10 mg/kg p.o.) normalized stress-induced defecation in a dose-dependent manner, whereas the 5-HT_{1A} agonist tandospirone (30 and 100 mg/kg p.o.) and the 5-HT₃ antagonist alosetron (1-10 mg/kg p.o.) did not show such effects. Furthermore, this efficacy of TZB-30878 was partly antagonized by a 5-HT_{1A} antagonist, [O-methyl-3H]-N-(2-(4-(2-methoxyphenyl)-1-piperazinyl)ethyl)-N-(2-pyridinyl)cyclohexanecarboxamide trihydrochloride (WAY-100635). These results suggest that 5-HT_{1A} receptor agonism and 5-HT₃ receptor antagonism contribute to the efficacy of TZB-30878 in the IBS-like model. The efficacy of TZB-30878 supports the concept that the presence of both actions, namely 5-HT_{1A} receptor agonism and 5-HT₃ receptor antagonism, could be an important mechanism in the treatment of d-IBS.

IT 864385-95-5

RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

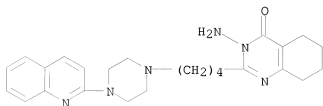
(pharmacol. properties of TZB-30878, a novel therapeutic agent for diarrhea-predominant irritable bowel syndrome (IBS) and its effects on an exptl. IBS model)

RN 864385-95-5 CAPLUS

CN 4(3H)-Quinazolinone, 3-amino-5,6,7,8-tetrahydro-2-[4-[4-(2-quinolinyl)-1-

10/513699

piperazinyl]butyl]- (CA INDEX NAME)



REFERENCE COUNT:

39

THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2005:979639 CAPLUS

DOCUMENT NUMBER: 143:286443

TITLE: Preparation of pyrimidine derivatives as 5-HT3
receptor antagonists having agonistic activity on
5-HT1AINVENTOR(S): Sato, Michitaka; Matsui, Teruaki; Asagarsu, Akira;
Hayashi, Hiroyuki; Araki, Seiichi; Tamaoki, Satoru;
Takahashi, Nobuyuki; Yamauchi, Yukinao; Yamamoto,
Yoshiko; Yamamoto, Norio; Ogawa, Chisato

PATENT ASSIGNEE(S): Teikoku Hormone Mfg. Co., Ltd., Japan

SOURCE: PCT Int. Appl., 261 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: Japanese

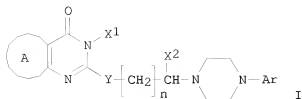
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005082887	A1	20050909	WO 2005-JP3691	20050225
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RW:	BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
AU 2005217320	A1	20050909	AU 2005-217320	20050225
CA 2557541	A1	20050909	CA 2005-2557541	20050225
EP 1724267	A1	20061122	EP 2005-719969	20050225
R:	AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR			
CN 1922171	A	20070228	CN 2005-80005603	20050225
KR 2006127156	A	20061211	KR 2006-717068	20060824
US 20070197551	A1	20070823	US 2006-590707	20060825
PRIORITY APPLN. INFO.:			JP 2004-52040	A 20040226
			JP 2004-322858	A 20041105
			WO 2005-JP3691	W 20050225

OTHER SOURCE(S): MARPAT 143:286443

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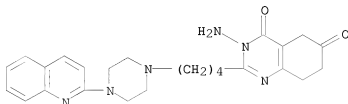
AB Title compds. I [ring A = carbocyclic group, etc.; X1 = H, amino, etc.; X2 = H, alkyl; Y = bond, etc.; n = 0-4; Ar = optionally substituted II with halo, etc.; Z = O, etc.; B = moiety required for completing mono-, ploy-heterocyclic ring containing N together with N-C-Z; dotted line indicates single, double bond] were prepared. For example, treatment of potassium 3-amino-5,6-dimethyl-4-oxo-3,4-dihydrothieno[2,3-d]pyrimidine-2-thiolate with 2-[4-(3-chloropropyl)piperazin-1-yl]quinoline, e.g., prepared from piperazine in 2 steps, afforded 3-amino-5,6-dimethyl-2-[3-(4-quinolin-2-ylpiperazin-1-yl)propylthio]-3H-thieno[2,3-d]pyrimidin-4-one (III) in 50% yield. In 5-HT3 receptor affinity assay (in vitro), compound III exhibited the antagonistic activity of 94% at 10⁻⁷ M. Compds. I are claimed useful for the treatment of anxiety, depression, etc. Formulation is given.

IT 864386-62-9P

RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of pyrimidine derivs. as 5-HT3 receptor antagonists having agonistic activity on 5-HT1A for treatment of anxiety, depression, etc.)

RN 864386-62-9 CAPLUS

CN 4,6-Quinazolinedione, 3-amino-3,5,7,8-tetrahydro-2-[4-[4-(2-quinolinyl)-1-piperazinyl]butyl]- (CA INDEX NAME)



IT 864385-95-5P 864385-96-6P 864385-97-7P
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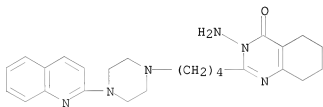
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RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of pyrimidine derivs. as 5-HT₃ receptor antagonists having agonistic activity on 5-HT_{1A} for treatment of anxiety, depression, etc.)

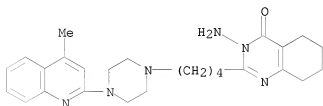
RN 864385-95-5 CAPLUS

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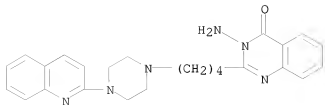
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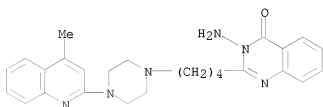
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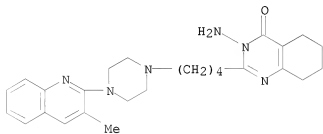
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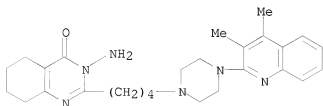
RN 864385-99-9 CAPLUS

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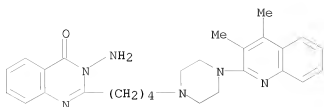
RN 864386-00-5 CAPLUS

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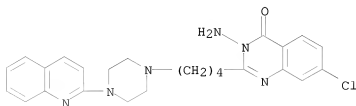


RN 864386-03-8 CAPLUS

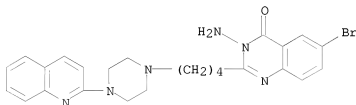
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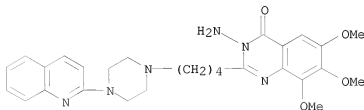
RN 864386-09-4 CAPLUS
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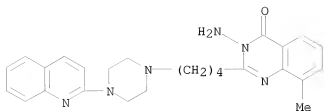
RN 864386-10-7 CAPLUS
 CN 4(3H)-Quinazolinone, 3-amino-6-bromo-2-[4-[4-(2-quinolinyl)-1-piperazinyl]butyl]- (CA INDEX NAME)



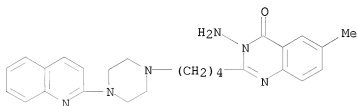
RN 864386-11-8 CAPLUS
 CN 4(3H)-Quinazolinone, 3-amino-6,7,8-trimethoxy-2-[4-[4-(2-quinolinyl)-1-piperazinyl]butyl]- (CA INDEX NAME)



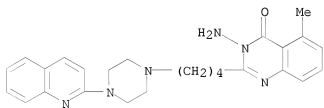
RN 864386-13-0 CAPLUS
 CN 4(3H)-Quinazolinone, 3-amino-8-methyl-2-[4-[4-(2-quinolinyl)-1-piperazinyl]butyl]- (CA INDEX NAME)



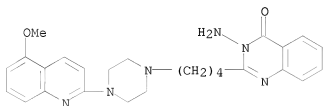
RN 864386-14-1 CAPLUS
 CN 4(3H)-Quinazolinone, 3-amino-6-methyl-2-[4-[4-(2-quinolinyl)-1-piperazinyl]butyl]- (CA INDEX NAME)



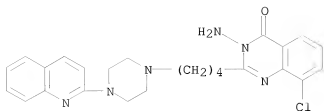
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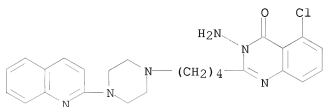
RN 864386-16-3 CAPLUS
 CN 4(3H)-Quinazolinone, 3-amino-2-[4-[4-(5-methoxy-2-quinolinyl)-1-piperazinyl]butyl]- (CA INDEX NAME)



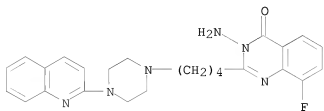
RN 864386-18-5 CAPLUS
 CN 4(3H)-Quinazolinone, 3-amino-8-chloro-2-[4-[4-(2-quinolinyl)-1-piperazinyl]butyl]- (CA INDEX NAME)



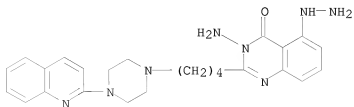
RN 864386-19-6 CAPLUS
 CN 4(3H)-Quinazolinone, 3-amino-5-chloro-2-[4-[4-(2-quinolinyl)-1-piperazinyl]butyl]- (CA INDEX NAME)



RN 864386-21-0 CAPLUS
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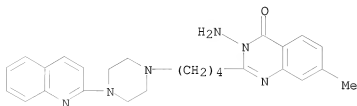


RN 864386-22-1 CAPLUS
 CN 4(3H)-Quinazolinone, 3-amino-5-hydrazinyl-2-[4-[4-(2-quinolinyl)-1-piperazinyl]butyl]- (CA INDEX NAME)



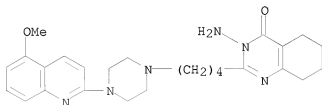
RN 864386-23-2 CAPLUS
 CN 4(3H)-Quinazolinone, 3-amino-7-methyl-2-[4-[4-(2-quinolinyl)-1-piperazinyl]butyl]- (CA INDEX NAME)

piperazinyl]butyl]- (CA INDEX NAME)



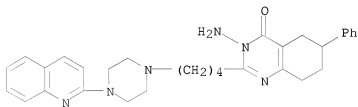
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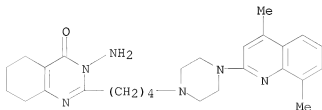
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CN 4(3H)-Quinazolinone, 3-amino-5,6,7,8-tetrahydro-6-phenyl-2-[4-[4-(2-quinolinyl)-1-piperazinyl]butyl]- (CA INDEX NAME)



RN 864386-27-6 CAPLUS

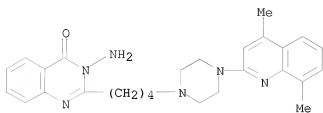
CN 4(3H)-Quinazolinone, 3-amino-2-[4-[4-(4,8-dimethyl-2-quinolinyl)-1-piperazinyl]butyl]-5,6,7,8-tetrahydro- (CA INDEX NAME)



RN 864386-28-7 CAPLUS

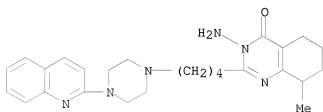
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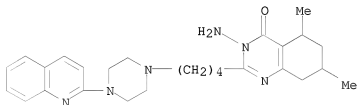
RN 864386-30-1 CAPLUS

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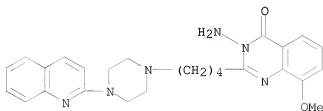
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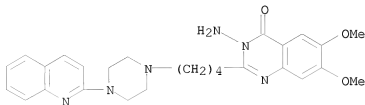
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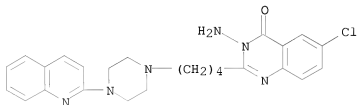


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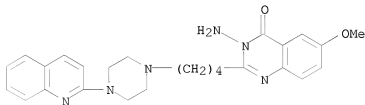
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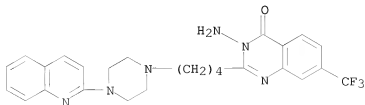
RN 864386-45-8 CAPLUS
CN 4(3H)-Quinazolinone, 3-amino-6-chloro-2-[4-[4-(2-quinolinyl)-1-piperazinyl]butyl]- (CA INDEX NAME)



RN 864386-46-9 CAPLUS
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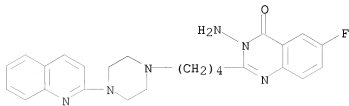
RN 864386-47-0 CAPLUS
CN 4(3H)-Quinazolinone, 3-amino-2-[4-[4-(2-quinolinyl)-1-piperazinyl]butyl]-7-(trifluoromethyl)- (CA INDEX NAME)



RN 864386-49-2 CAPLUS

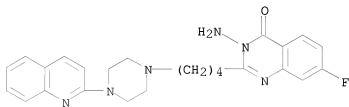
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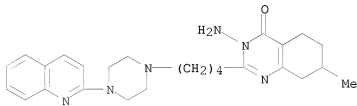
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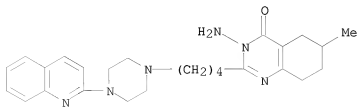
RN 864386-52-7 CAPLUS

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RN 864386-53-8 CAPLUS

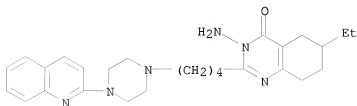
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RN 864386-54-9 CAPLUS

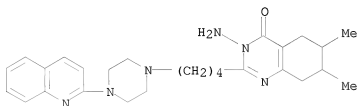
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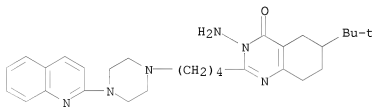
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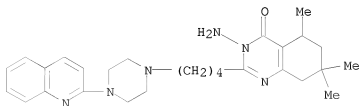
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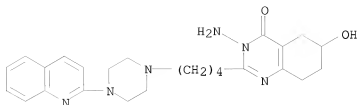
RN 864386-57-2 CAPLUS

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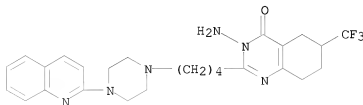
RN 864386-63-0 CAPLUS

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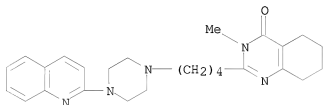
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CN 4(3H)-Quinazolinone, 3-amino-5,6,7,8-tetrahydro-2-[4-[4-(2-quinolinyl)-1-piperazinyl]butyl]-6-(trifluoromethyl)- (CA INDEX NAME)



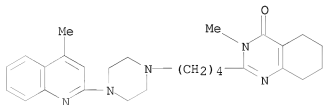
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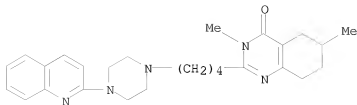
RN 864386-81-2 CAPLUS

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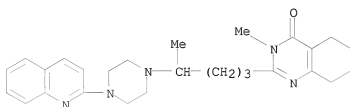
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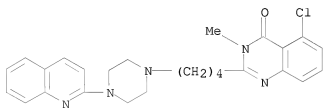
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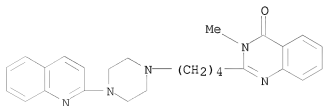
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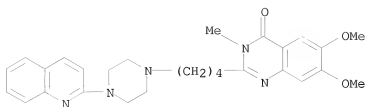
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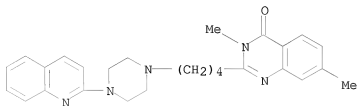


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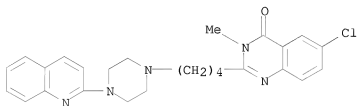
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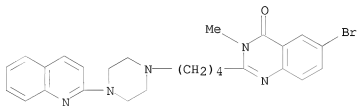
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RN 864387-00-8 CAPLUS
 CN 4(3H)-Quinazolinone, 6-chloro-3-methyl-2-[4-[4-(2-quinolinyl)-1-piperazinyl]butyl]- (CA INDEX NAME)



RN 864387-01-9 CAPLUS
 CN 4(3H)-Quinazolinone, 6-bromo-3-methyl-2-[4-[4-(2-quinolinyl)-1-piperazinyl]butyl]- (CA INDEX NAME)



REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

10/513699

=> FIL STNGUIDE
COST IN U.S. DOLLARS

SINCE FILE	TOTAL
ENTRY	SESSION
18.27	196.84

FULL ESTIMATED COST

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)

SINCE FILE	TOTAL
ENTRY	SESSION
-2.40	-2.40

CA SUBSCRIBER PRICE

FILE 'STNGUIDE' ENTERED AT 14:55:32 ON 19 DEC 2008
USE IS SUBJECT TO THE TERMS OF YOUR CUSTOMER AGREEMENT
COPYRIGHT (C) 2008 AMERICAN CHEMICAL SOCIETY (ACS)

FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Dec 12, 2008 (20081212/UP).

=> d his

(FILE 'HOME' ENTERED AT 14:52:33 ON 19 DEC 2008)

L1 FILE 'REGISTRY' ENTERED AT 14:52:45 ON 19 DEC 2008
L2 STRUCTURE UPLOADED
51 S L1 FULL

L3 FILE 'CAPLUS' ENTERED AT 14:53:25 ON 19 DEC 2008
3 S L2 FULL

FILE 'STNGUIDE' ENTERED AT 14:55:32 ON 19 DEC 2008

=> log y
COST IN U.S. DOLLARS

SINCE FILE	TOTAL
ENTRY	SESSION
0.12	196.96

FULL ESTIMATED COST

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)

SINCE FILE	TOTAL
ENTRY	SESSION
0.00	-2.40

CA SUBSCRIBER PRICE

STN INTERNATIONAL LOGOFF AT 14:56:35 ON 19 DEC 2008